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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/707,117	WOLFF ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,7,11,12,16-20,24,25,28-31,34-36 and 39-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,11,12,16-20,24,25,28-31,34-36 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 6-16-04 have been fully considered but they are not persuasive. Claim 38 has been canceled. Overall, claims 4, 5, 8-10, 13-15, 21-23, 26, 27, 32, 33, 37 and 38 have been canceled. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 remain pending and under consideration. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

In claim 35, delete "around the limb" to be more clear. Applicants point to support for the phrase but do not address the objection. The phrase is ambiguous because it can be interpreted as "near" the limb or as around the limb without touching.

The other objections have been withdrawn in view of the amendments to the claims.

Claim 1, step a) is newly objected to because the phrase "inserting the polynucleotide in a solution into a blood vessel in the limb" does not clearly parallel the preamble of the claim, which refers to "delivering a polynucleotide to a skeletal muscle cell in a limb of a mammal," or reflect the polynucleotide is injected into the mammal *in vivo.* Step 1 a) should be clearly set forth as "inserting a polynucleotide into a blood vessel in a limb of a mammal *in vivo*". The preamble can then be limited to a "process for delivering a polynucleotide to skeletal muscle cells of a mammal *in vivo*".

Claim 39, step a) is newly objected to because the phrase "inserting the polynucleotides into a blood vessel in the limb of the mammal" does not clearly parallel the preamble of the claim, which refers to "an *in vivo* process for delivering polynucleotides to skeletal muscle cells in a limb of a mammal," or reflect the polynucleotide is injected into the mammal *in vivo.* Step 39 a) should be clearly set forth as "inserting a polynucleotide into a blood vessel in a limb of a mammal *in vivo*". The preamble can then be limited to a "process for delivering a polynucleotide to skeletal muscle cells of a mammal *in vivo*".

Claim 39, step b) is objected to because it is wordy. The phrase "applying pressure to the limb wherein the pressure is applied non-invasively against the skin of the limb" is equivalent to "applying pressure [to the limb wherein the pressure is applied] non-invasively against the skin of the limb".

The phrase "and expressing the polynucleotide" in claim 39, lines 10-11, does not make sense in the claim because the step of "expressing" has been deleted. The phrase "wherein inserting the polynucleotide, applying pressure" should more clearly refer to steps a) and b), e.g. "wherein said inserting and said applying do not diminish..." or "wherein steps a) and b) do not diminish...."

Claim Rejections - 35 USC ' 112

New Matter

The limitation of applying external pressure against the mammal's skin is found on pg 3, ¶ 2.

The rejection regarding the phrase "immunosuppressive treatment" in claim 1 as new matter has been withdrawn in view of pg 3, lines 26-32. The new phrase "administering immunosuppressive drugs" in claim 1 also has support on pg 3, lines 26-32.

The rejection regarding the terms "superficialis" and "profundus" (12) has been withdrawn because it would have been readily apparent that flexor digitorum spf. And flexor digitorum prof. on pg 26 must have referred to flexor digitorum superficialis and flexor digitorum profundis. No other flexor digitorum muscles could have such abbreviations.

The rejection regarding the limitations of "applying a tourniquet around the limb" (34), "applying a cuff around the limb" (35) has been withdrawn because a sphygmomanometer surrounding the limb as on pg 5, lines 5-11, pg 25, lines 19-21 and a tourniquet applied around the limb on pg 32, lines 22-24, support the limitations.

The rejection regarding impeding "blood flow to the limb" in claim 39, step a) has been withdrawn because the sphygmomanometer, cuff or tourniquet described on pg 5, lines 5-11 and pg 32, lines 22-24, implicitly impede blood flow to the limb. The new phrase "impeding blood flow into and out of the limb" also has implicit support on pg 5, lines 5-11, and pg 32, lines 22-24.

The rejection regarding delivering polynucleotides to the skeletal muscle cells of the limb distal to the applied pressure in claim 39, step b) has been withdrawn. Pg 23, lines 22-24, teaches impeding blood flow of the arm or leg with a sphygmomanometer cuff "proximal to the injection site," which implicitly means the polynucleotides were injected distal to the cuff.

The rejection regarding the phrase "does not diminish the use of the limb by the mammal" in claim 39 has been withdrawn. Pg 3, lines 16-17, states, "it is important that the full function of the mammal's limbs subsequent to delivery is maintained using this process." Pg 25, lines 17-25, states monkeys receiving injections with a cuff did not have diminished the use of the limb after the procedure. Pg 3, lines 16-17, and pg 25, lines 17-25, implicitly support the phrase.

The rejection regarding the phrase "a single treatment" in claim 41 has been withdrawn because the phrase has been deleted.

The new phrase "administering immunosuppressive drugs within one day of injecting the polynucleotide" in claim 41, has support on pg 28, line 27, through pg 29, line 5, and pg 31, lines 13-15. Pg 28, line 27, through pg 29, line 5, taught intravascular injection of DNA into rats treated with "2.5 mg/kg of FK506 orally and 1 mg/kg dexamethasone subcutaneously one day prior to, one hour prior to and every day thereafter with FK506" or "with 10 mg/kg of FK506 orally and 1 mg/kg dexamethasone subcutaneously one day prior to, one hour prior to and one day after intraarterial

delivery of pDNA". Each condition requires at least three injections of FK506 or dexamethasone within one day of administering the DNA. Pg 31, lines 13-15, also requires at least three injections within one day of administering the DNA.

1. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 as newly amended are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The term "non-invasive" in claims 1 and 39 is new matter. No explicit support can be found. "Invasive" can be defined two different ways. 1) "denoting a procedure requiring insertion of an instrument or device into the body through the skin or a body orifice..." (see Stedman's Medical Dictionary definition attached) or 2) "to affect injuriously and progressively" (see Merriam-Webster Online Dictionary definition attached). The specification does not implicitly support applying pressure without inserting an instrument or device into the body through the skin. It is not readily apparent that the pressure applied in Example 1 was applied without "inserting an instrument into the body through the skin" because the cuff was applied while the inside of the leg was exposed; it is not readily apparent that the cuff was applied outside of the surgical area. The specification also describes using clamps (Example 8) which are inserted inside the leg but do not cause damage to the leg. Therefore, the specification

does not implicitly support applying pressure without insertion of an instrument or device into the body as encompassed by "non-invasive."

Enablement

The rejection regarding delivering a polynucleotide to the specific muscle cells in claims 11, 12, 17, 24, 25 and 29-31 has been withdrawn because the claims are limited to injecting a limb with a polynucleotide and delivering the polynucleotide to skeletal muscle cells of the same limb. Example 10 taught injecting the upper portion of a rat leg with a plasmid and obtaining delivery of the plasmid to a foot skeletal muscle in the rat leg. Example 1 on pg 23 teaches injecting plasmid into the arm or leg of a monkey by inserting a catheter into the brachial artery of the arm or the political artery of the leg, and cuffing the arm or leg proximal to the injection site (closer to the trunk). Example 3 on pg 26-27 shows the skeletal muscle cells distal to the site of injection showed luciferase expression – an indication that the plasmid was delivered to the skeletal muscle cells of the limb injected distal to the site of injection.

2. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel, wherein said DNA comprises a nucleic acid sequence encoding a protein

operably linked to a promoter and wherein said protein is expressed to detectable levels in muscle cells of said limb, does not reasonably provide enablement for 1) injecting the polynucleotide to the limb proximally to the applied pressure and obtaining delivery of the polynucleotide to the skeletal muscle cells of the limb distally to the applied pressure; 2) expressing a polynucleotide in skeletal muscle cells by injecting a viral vector into a blood vessel of a limb and applying a cuff proximal to the site of injecting; or 3) administering any polynucleotide as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claim 1 requires applying pressure to a limb so that blood flow is impeded, and injecting a polynucleotide into a blood vessel of the limb, "such that the polynucleotide is delivered to the skeletal muscle cell in the limb distal to the applied non-invasive pressure." As such, claim 1 encompasses injecting the polynucleotide to the limb proximally to the applied pressure and obtaining delivery of the polynucleotide to the skeletal muscle cells of the limb distally to the applied pressure. I.e. claim 1 is not limited to injecting the polynucleotide distal to the applied pressure.

Claim 3 encompasses injecting a viral vector into a blood vessel of a limb to obtain delivery to a skeletal muscle cell.

Claims 6, 7, 11, 12, 16-20, 24, 25 and 28-31 require delivery to skeletal muscle cells of limbs, some of which require delivery to specific muscles within the limbs.

Claim 39 requires applying pressure to a limb so that blood flow is impeded, and inserting a polynucleotide into a blood vessel of the limb, "such that the polynucleotides are delivered to the skeletal muscle cells of the limb distal to the applied pressure." As such, claim 39 encompasses injecting the polynucleotide to the limb proximally to the applied pressure and obtaining delivery of the polynucleotide to the skeletal muscle cells of the limb distally to the applied pressure. I.e. claim 39 is not limited to injecting the polynucleotide distal to the applied pressure.

Vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art (Miller of record, 1995, FASEB J., Vol. 9, pages 190-199; Deonarain of record, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69; pg 53, 1st ¶; pg 65, 1st ¶, under Conclusion section; Verma of record, Sept. 1997, Nature, Vol. 389, pg 239-242; see entire article; pg 240, sentence bridging col. 2 and 3; Crystal of record, 1995, Science, Vol. 270, pg 404-410; pg 409).

The specification does not enable delivering the polynucleotide to a blood vessel of a limb proximal to the applied pressure and delivering the polynucleotide to skeletal muscle cells of the limb distal to the applied pressure as broadly encompassed by claims 1 and 39. For example, the specification does not teach delivering DNA to a blood vessel in the upper leg with a cuff around the knee and obtaining delivery of the

polynucleotide in muscle cells of the foot. In fact, the applied pressure would prevent delivery of the polynucleotide from the upper leg to the foot. It would have required one of skill in the art at the time the invention was made undue experimentation to determine the parameters required to deliver DNA to skeletal muscle distal to the applied pressure as broadly claimed. Therefore, claims 1 and 39 should be limited to injecting the polynucleotide distal to the site of applied pressure.

The specification does not enable one of skill to apply a tourniquet to the limb and inject a viral vector into a blood vessel of a limb distal to the tourniquet to obtain expression of a protein encoded by the vector in skeletal muscle cells (claim 3). Milas of record (Dec. 1997, Clin. Cancer Res., Vol. 3, pg 2197-2203) taught injecting adenoviral particles to a femoral artery and vein occluded using a tourniquet passed under the inguinal ligament proximal to the site of injecting; however, the method did not result in expression in the muscle cells of limb (pg 2198, Fig. 1A and B, see legend and tourniquet in Fig. 1A; pg 2201, col. 2, 1st full ¶). Ye of record (March 1, 2000, Human Gene Therapy, Vol. 11, pg 621-627) also taught administering adenoviral particles encoding LacZ to the portal vein/artery occluded with clamps did not result in expression in skeletal muscle. While the tourniquet described in the instant application is not passed under the inguinal ligament as taught by Milas, applicants have not correlated the obtained results of Milas with expected results obtained when the perfusion pump is not used and the tourniquet is not passed under the inguinal

ligament. The difference between passing the tourniquet under the inguinal ligament and not passing the tourniquet under the inguinal ligament would be insignificant to one of skill in the art. It is not readily apparent that injecting an adenovirus using the method in claim 1 (applying a cuff, injecting the vector 5 minutes later and removing the cuff two minutes later) would cause protein expression because Milas taught an adenovirus perfusing through the leg for 13 minutes did not cause expression (pg 2199, col. 1, 2nd full ¶, last sentence).

The specification does not provide adequate guidance for one of skill to determine why or when an immunosuppressive agent is administered, when an immunosuppressive agent is required to obtain expression in the desired skeletal muscle cell, how administering such an agent effects the delivery of DNA or whether different immunosuppressive agents have different effects on the delivery of DNA.

The specification does not enable delivering any polynucleotide as broadly claimed. The specification only teaches delivering DNA encoding a marker protein operably linked to a promoter. The specification does not enable delivering any other polynucleotide or delivering DNA encoding a marker protein in the absence of a promoter.

Applicants' argue Miller, Deonarain, Verma and Crystal do not contemplate the process taught by applicants. Therefore, applicants conclude that progress has been made in the field of gene therapy by applicants, and Miller, Deonarain, Verma and

Crystal cannot be given weight to support an argument that applicants' process cannot work. Applicants' argument is not persuasive. Applicants have not addressed the claims, which encompass injecting a limb with polynucleotides proximal to applied pressure and obtaining delivery distal to the applied pressure. Applicants have not overcome the unpredictability of targeting polynucleotides to the desired tissue established by Miller, Deonarain, Verma and Crystal by teaching how to inject a limb with polynucleotides proximal to applied pressure and obtaining delivery of the polynucleotides distal to the applied pressure.

Applicants have repeated the argument that Milas and applicants invention are distinct. Again, the argument is not persuasive because it is misplaced under enablement (pg 8 of response filed 3-3-04, 2nd full ¶). Applicants have not provided any reason why Milas enables applicants' invention as broadly claimed.

Applicants argue Ye taught a method that is different than the method taught by applicants. Applicants' argument is not persuasive. Milas and Ye established the inability to obtain expression of proteins in muscle tissue using adenovirus and a clamped blood vessel. Ye taught it was unknown how far the viral vector would be delivered when administered to the portal vein, i.e. injecting a blood vessel with a viral vector in vivo may not result in delivery of the viral vector to skeletal muscle cells. While Ye injected the portal vein and applicants' claims are limited to injecting the limb, one of skill would not conclude that delivery of the viral vector to skeletal muscle cells would

occur. The art and the specification did not teach how far a viral vector will go when injected into the limb or that adequate amounts of the viral vector would go to skeletal muscles such that expression was detectable when injected into the limb.

Applicants argue the results obtained with naked plasmid DNA correlates to other vectors such as adenovirus. Applicants again point to the declaration filed 5-9-03, which was found unpersuasive because the teachings in the declaration were not present in the specification and were essential to perform the method using adenovirus. Applicants argue the teachings in the declaration were present in the specification as originally filed. Applicants' arguments are not persuasive.

The combination of elements required to target the tissue of interest using adenovirus is essential to the claimed invention (based on Miller, Verma, Crystal, Deonarain, and Ye all of record). The specification suggests using papaverine (pg 5, lines 26-28; ¶ bridging pg 16-17) and "an enzyme [that] could digest the extracellular material" (¶ bridging pg 16-17). It is not readily apparent from the specification that applicants considered using both papaverine and collagenase as described in the declaration because the paragraph bridging pg 16-17 and pg 5, lines 26-28 only suggest using one compound that is papaverine or an enzyme and because Examples 1 and 8 only used papaverine. Example 8 does not correlate to the results described in the declaration because example 8 required plasmid DNA and did not use collagenase while the declaration taught injecting $\underline{5x10^8}$ adenoviral particles/10 ml saline within 10

seconds after papaverine and collagenase. It is not readily apparent that merely replacing the plasmid in Example 8 with adenovirus would provide the results described in Example 8 in the absence of collagenase. The concentration of $5x10^8$ adenoviral particles/10 ml saline described in the declaration is not taught anywhere in the specification and is not readily apparent from the teachings of the specification. Pg 17, line 9, to pg 18, line 6, only describe the injection volume (ml, ml/body weight, ml/liver weight or ml/limb muscle weight) and the speed at which a vector is injected. Pg 17, line 9, to pg 17, line 25, do not correlate to the results described in the declaration because they are limited to injection volumes for non-viral vectors. In conclusion, the specification does not reasonably lead one of skill to the specific combination of injecting $5x10^8$ adenoviral particles/10 ml saline within 10 seconds after papaverine and collagenase. Therefore, the specification does not teach the essential elements required to obtain the results described in the declaration.

In addition, the claims are not limited to delivering adenovirus, or to delivering adenovirus in combination with papaverine and collagenase before injection, or to injecting the adenovirus within 10 seconds. Therefore, the data in the declaration does not correlate to the claims because the data in the declaration only represents a small species within the genus claimed.

Applicants argue the specification on pg 3, lines 27-28 and Example 5 on pg 28 describe when immunosuppression drugs are administered. Applicants' argument is

not persuasive. Pg 3, line 27-28, does not teach how to obtain immunosuppression for a "long term or for a short duration, preferably around the time of the nucleic acid delivery." While Example 5 shows animals receiving immunosuppression showed expression of the gene for a longer period of time, the schedule for administering dexamethasone with FK506 is unclear. The paragraph bridging pg 28-29 states the rats were treated with "2.5 mg/kg of FK506 orally and 1 mg/kg dexamethasone subcutaneously one day prior to, one hour prior to and every day thereafter with FK506." Administering FK506 and dexamethasone in combination with administering FK506 "every day thereafter" does not make sense. It cannot be determined if FK506 and dexamethasone were administered together one day prior to injection, together one hour prior to injection and together every day after injection or if FK506 was injected every day after injection in the absence of dexamethasone. Thus, the specification does not teach how to obtain the results when transient immunosuppression is required. In addition, Example 5 does not describe when immunosuppression is required for delivery to the specific skeletal muscles of claims 11, 12, 16, 17, 24, 25 or 29-31 because the results of Example 5 are generic to expression of luciferase in the muscles of the entire hind limb. Therefore, applicants do not provide adequate guidance to determine when immunosuppression is required to obtain delivery to specific skeletal muscle cells using the claimed invention.

Applicants argue the specification enables more than delivering DNA encoding a marker protein operably linked to a promoter. Applicants argue a therapeutic gene is functionally equivalent to marker gene for the purposes of delivery using the method claimed. Applicants' argument is persuasive in part. Pg 9, lines 8-12, teach delivering gene products such as growth hormone, factor IX, etc to determine the amount of a secreted protein that a gene delivery procedure can produce and that "the reporter gene product can be assayed in a small amount of blood." Example 8, pg 31, teaches delivering plasmid encoding Factor IX to determine the amount of secreted protein in the sera and muscle. Therefore, the specification supports using therapeutic genes as marker proteins for delivery to skeletal muscle cells to determine the amount of therapeutic protein expressed in skeletal muscle cells. However, the genes described in the specification all require a nucleic acid sequence encoding a protein operably linked to a promoter. This is found in the Factor IX gene in example IX and the marker genes described throughout the examples. Therefore, the claims should be limited to a nucleic acid sequence encoding a protein operably linked to a promoter.

Applicants argue the polynucleotide does not have to encode a protein because it can encode an RNA molecule that is not translated into protein but has a cellular function itself. RNA not translated into protein would not be "expressed in the skeletal muscle cell" as claimed. The specification does not describe the polynucleotide recited in claims 1 or 39 as encompassing an RNA molecule that is not translated into protein

"but has a cellular function itself." Therefore, the claims should be limited to DNA encoding a protein operably linked to a promoter.

Indefiniteness

The rejection regarding "the mammal's skin" in claim 1 b) has been withdrawn in view of the amendment.

The rejection regarding whether administering immunosuppressive treatment (c) may be the result of the applying pressure to the skin in step (b) or if administering immunosuppressive treatment must be a new, separate step has been withdrawn because step b) has been limited to administering immunosuppressive drugs.

The rejection regarding the phrase "wherein delivery of the polynucleotide to the limb skeletal muscle cells results in expression" in claim 1 has been withdrawn in view of the amendment to the claim.

The rejection regarding the phrase "delivery of the polynucleotide to the limb skeletal muscle cell" having the same scope as "results in expression of the polynucleotide at detectable levels" in claim 1 has been withdrawn in view of the amendment to the claim.

The rejection regarding claims 34 and 35 because "applying pressures" does not have proper antecedent basis has been withdrawn in view of the amendments to the claims.

The rejection regarding claim 38 because delivery to "non-vascular parenchymal cells" does not further limit delivery to the "limb skeletal muscle cell" as in parent claim 1 has been withdrawn because claim 38 has been cancelled.

The rejection regarding impeding "blood flow to the limb" as in claim 39, step a) has been withdrawn because the phrase has been amended to "blood flow into and out of the limb" and because the sphygmomanometer, cuff or tourniquet described on pg 5, lines 5-11 and pg 32, lines 22-24, implicitly impede blood flow to the limb. The new phrase "impeding blood flow into and out of the limb" is also clear from pg 5, lines 5-11, and pg 32, lines 22-24.

The rejection regarding "distal to" in claim 39, step b) has been withdrawn because "distal" means "away from the center of the body or from the point of origin... ...the distant part of a limb..." (see Stedman's Medical Dictionary definition of "distal" enclosed). The polynucleotides are delivered to the distant part of the limb as compared to the site where pressures is applied to the limb.

The rejection of claim 39 regarding the phrase "delivering the polynucleotide to mammalian skeletal muscle cells" (step b) has been withdrawn in view of the amendment.

The rejection of claim 40 because "repetitive treatment" does not make sense has been withdrawn in view of the amendment.

3. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The phrase "applying non-invasive pressure" in claims 1 and 39 is indefinite. "Invasive" can be defined two different ways. 1) "denoting a procedure requiring insertion of an instrument or device into the body through the skin or a body orifice..." (see Stedman's Medical Dictionary definition attached) or 2) "to affect injuriously and progressively" (see Merriam-Webster Online Dictionary definition attached). The specification does not teach which definition to use. It is not readily apparent that the methods used by applicants do not require inserting an instrument into the body through the skin because the cuff described in Example 1 was applied during a surgical procedure. It is not readily apparent that the cuff was applied outside of the surgical area. Therefore, it cannot be determined whether pressure that does not cause injury to the leg is encompassed by the phrase.

Claim 1 as newly amended is indefinite. It is unclear if the claim is intended to encompass injecting the polynucleotide anywhere in the limb and obtaining delivery distal to the site of applying pressure or if the claim is limited to injecting the polynucleotide into the limb distal to the site of applying pressure and obtaining delivery of the polynucleotide distal to the site of applying pressure.

The phrase "wherein inserting the polynucleotide, applying pressure, and expressing the polynucleotide does not diminish subsequent use of the limb by the mammal" in claim 39 remains unclear. It is unclear if the phrase is limited to the function of the limb after the procedure or if the phrase encompasses the diminished frequency of use of the limb. Applicants point out that pg 3, lines 13-19, and pg 25, lines 17-25, support the phrase and conclude that the phrase "encompasses both the functional parameters of the lib and the frequency of use of the limb"; however, applicants have provided no arguments. The citations do not clarify the issue. Pg 3 refers to maintaining the function of the limbs after delivery of polynucleotides and applying pressure. Pg 25, lines 17-25, also refers to maintaining the function of the limbs after delivery of polynucleotides and applying pressure. It is not readily apparent from the specification that pg 3 or pg 25 encompasses the frequency of use of the limb.

Claim Rejections - 35 USC ' 102

The rejection of claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 40-42 under 35 U.S.C. 102(e) as being anticipated by Draijer-van der Kaaden (US Patent 6,495,131) has been withdrawn because a tourniquet is not an immunosuppressive drug as newly claimed.

The rejection of claims 1, 3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36, 40 and 41 under 35 U.S.C. 102(b) as being anticipated by Milas (Dec. 1997, Clin. Cancer Res.,

Vol. 3, pg 2197-2203) has been withdrawn because a tourniquet is not an immunosuppressive drug as newly claimed.

The rejection of claim 39 under 35 USC 102(b) as being anticipated by Milas (Dec. 1997, Clin. Cancer Res. Vol. 3,pg 2197-2203) has been withdrawn because the method taught by Milas did not result in expression of the protein in skeletal muscle cells as now required in claim 39. Milas taught administering adenoviral particles to an occluded femoral artery and vein of a rat (using a tourniquet applied to the skin of the leg (pg 2198, Fig. 1A, see tourniquet on rat)). While the tourniquet of Milas most definitely impedes inflow and outflow of blood through the limb as claimed, Milas allows outflow of blood using the perfusion pump. This is different than applicants' method in Example 10, which impedes all blood flow into and out of the limb and does not involve perfusion. While the method of Milas inherently caused DNA to be delivered to skeletal muscle cells as claimed (because the method taught by Milas used a tourniquet as described in Example 10), Milas clearly states the method did not cause expression of the protein in skeletal muscle (pg 2201, col. 2, 1st full ¶).

The rejection of claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 40-42 under 35 U.S.C. 102(a) as being anticipated by Von der Leyen (9-20-99, Human Gene Therapy, Vol. 10, pg 2355-2364) has been withdrawn because a tourniquet is not an immunosuppressive drug as newly claimed.

4. Claim 39 remains rejected under 35 USC 102(e) as being anticipated by Draijer-van der Kaaden (US Patent 6,495,131). '131 has priority back to July 13, 1998.

Draijer-van der Kaaden taught administering adenovirus to the femoral vein using a tourniquet around the groin, and fixed to the inguinal ligament (detailed description, ¶ 25; col. 17, lines 1-55). The adenovirus was perfused through the leg using a pump. The tourniquet impeded blood flow into and out of the blood vessel as claimed because it was wrapped around the leg and blocked the blood vessels. The tourniquet was "non-invasive" as claimed because it did not injure the leg. The method of Draijer-van Kadden inherently resulted in delivery and expression in skeletal muscle cells as claimed because the adenovirus was perfused for 5 to 30 minutes (col. 17, line 19) and expression was obtained in a tumor at a distance away from the blood vessel.

Applicants argue Draijer-van der Kaaden taught outflow was required for successful perfusion and concludes that Draijer-van der Kaaden does not teach impeding blood flow into and out of the limb as claimed. Applicants' argument is not persuasive. The tourniquet of Draijer-van der Kaaden impedes inflow and outflow of blood through the limb as claimed because it is around the leg and blocking blood vessels. The claim is not limited to impeding all blood flow out of the limb. The claim encompasses using a tourniquet in combination with the perfusion pump described by Draijer-van der Kaaden.

5. Claim 39 remains rejected under 35 U.S.C. 102(a) as being anticipated by Von der Leyen (9-20-99, Human Gene Therapy, Vol. 10, pg 2355-2364) for reasons of record.

Von der Leyen taught administering naked plasmid DNA into the carotid artery while applying a sphygmomanometer to the skin of the limb (pg 2356 col. 2, Transfection procedure; pg 2360, Fig. 2, see 300). The sphygmomanometer impedes inflow and outflow of blood to the limb. While Von der Leyen did not explicitly teach obtaining delivery to skeletal muscle as claimed, Von der Leyen implicitly taught obtaining delivery to skeletal muscle. Von der Leyen obtained expression in the layers of the carotid artery; therefore, the method of Von der Leyen inherently results in delivery beyond the blood vessel wall and into skeletal muscle as claimed because the carotid artery is surrounded by skeletal muscle. Inherency is also relied upon because Von der Leyen forced the DNA through the blood vessel wall (pg 2362, col. 1, line 14).

Applicants argue DNA forced through the blood vessel wall as taught by Von der Leyen would only cause delivery to the layers of the blood vessel and not out of the blood vessel wall. Applicants' argument is not persuasive. Von der Leyen used a 3 cm sheath around the blood vessel, but the catheter used to delivery the DNA was "placed at the distal end of the protected vessel" (pg 2356, col. 2, Transfection procedure, lines 1-5 and 8-14). Pg 2362, 2nd full ¶, lines 16-20, teach "With the exception of movements during which the initial pressurization takes place, there are no convective forces across

the vessel wall, and movement of solubles such as oligonucleotides or plasmid DNA is therefore driven by simple diffusion, as with the nonpressurized vessel." Therefore, applicants' conclusion (that a blood vessel surrounded by a 3 cm sheath would not allow DNA outside of the wall) is not true because DNA may be diffused through the wall during initial pressurization. In addition, DNA may also be diffused through blood vessel walls in areas not covered by the 3 cm sheath.

Applicants state the reason why Von der Leyen used the sphygmomanometer is relevant. Applicants argue the reason Von der Leyen used the sphygmomanometer to monitor the pressure of a solution. Applicants' argument is unfounded. The sphygmomanometer of Von der Leyen impedes blood flow into and out of the limb, which is all that is required in the claim.

Claim Rejections - 35 USC ' 103

The rejection of claims 1-3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36 and 39-42 under 35 U.S.C. 103(a) as being unpatentable over Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) in view of Nabel (US Patent 5,910,488, June 8, 1999) has been withdrawn because the method taught by Milas did not result in expression of protein in skeletal muscle cells as now required in claims 1 and 39. Milas taught administering adenoviral particles to a femoral artery and vein of a rat using a tourniquet applied to the skin of the leg that passed under the inguinal ligament (pg 2198, Fig. 1A,

see tourniquet on rat and legend). While the tourniquet of Milas impeded inflow and outflow of blood through the limb as claimed, the method of Milas did not cause expression of the protein in the skeletal muscle as claimed (pg 2201, col. 2, 1st full ¶). While the method of Milas inherently caused DNA to be delivered to skeletal muscle cells as claimed (because the method taught by Milas used a tourniquet as described in Example 10), the method of Milas did not cause expression of the protein in skeletal muscle as claimed.

6. Claims 1-3, 6, 11, 12, 16, 17, 28, 30, 31, 34 35, 36 and 39-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Budker (1998, Gene Therapy, Vol. 5, pg 272-276) in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) for reasons of record.

Budker taught administering naked plasmid DNA encoding marker protein into an artery in the leg of a rat, wherein pressure was applied to the artery using microvessel clips. Administration resulted in marker protein expression in skeletal muscle cells of the leg (pg 274, col. 2, 1st full ¶). Budker also taught injecting collagenase is also equivalent to applying immunosuppressive drugs because collagenase degrades the capillary membranes thereby decreasing the flow of blood through the immune system (i.e. immunosuppression). Budker did not teach applying pressure to the skin of the limb as claimed.

However, Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the epidermis of the leg (pg 2198, Fig. 1A, see tourniquet on rat).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into an artery in the leg of a rat using pressure to deliver and express the DNA in all the skeletal muscle cells of the leg as taught by Budker wherein pressure was applied using a tourniquet applied to the leg as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using microvessel clips with the tourniquet of Milas to reduce damage to the blood vessels and to eliminate time in surgery spent applying microvessel clips.

Applicants argue administering collagenase does not remove cells of the immune system from the limb or diminish the ability of the immune cells in the limb from carrying out their functions. Applicants' argument is not persuasive. The claims do not require removing cells of the immune system from the limb or diminishing the function of the immune cells in the limb. Collagenase suppresses the immune system (i.e. is "immunosuppressive") as claimed because it weakens the flow of blood by degrading capillary membranes. Collagenase suppresses the immune system by decreasing the normal flow of cells through the immune system.

Applicants argue the claims require impeding the blood flow to and from the limb and point out that the method of Milas allows outflow of blood because a perfusion pump is used. Therefore, applicants conclude Milas does not meet the limitation "blood flow to and from the limb is impeded" as claimed. Applicants' arguments are not persuasive. The claims are not limited to impeding all blood flow into and out of the limb. The tourniquet of Milas most definitely impedes blood flow into and out of the limb as claimed because it constricts the limb and applies pressure to all of the blood vessels of the limb. While Milas used a perfusion pump to allow some blood flow out of the limb, the claims do not exclude allowing some blood flow out of the limb.

Applicants argue the tourniquet of Milas is not "non-invasive" as claimed because it passed under the inguinal ligament. Applicants' argument is not persuasive. The tourniquet of Milas is "non-invasive" because it does not injure the leg. While the tourniquet passed under the inguinal ligament is in the surgical field, the tourniquet does not injure the leg, does not go inside the leg, and is not applied directly to blood vessels of the leg.

7. Claims 1-3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36 and 39-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (US Patent 6,265,387, July 24, 2001) in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203).

Wolff taught delivering naked plasmid DNA to a clamped femoral artery and obtaining expression in the quadriceps (col. 17, Example 8). Some of the animals

received subcutaneous administration of dexamethasone the day before surgery (col. 18, line 45), which is an immunosuppressive drug as, claimed. Wolff did not teach using a tourniquet.

However, Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the skin of the leg passed under the inguinal ligament (pg 2198, Fig. 1A, see tourniquet on rat and description in legend of Fig. 1B).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into an femoral artery of a rat using pressure to obtain expression in the quadriceps as taught by Wolff using a tourniquet applied to the skin of the leg as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using clamps of Wolff with using the tourniquet of Milas to reduce damage to the blood vessel and to eliminate time in surgery spent applying the clamps. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the adenoviral vector of Milas with the plasmid DNA of Wolff to prevent viral infection.

Applicants argue the claims require impeding the blood flow to and from the limb and point out that the method of Milas allows outflow of blood because a perfusion pump is used. Therefore, applicants conclude Milas does not meet the limitations of the claims. Applicants' arguments are not persuasive. The claims are not limited to

impeding all blood flow into and out of the limb. The tourniquet of Milas most definitely impedes blood flow into and out of the limb because it constricts the limb. While Milas used a perfusion pump to allow some blood flow out of the limb, the claims do not exclude allowing some blood flow out of the limb.

Applicants argue the tourniquet of Milas is not "non-invasive" as claimed because it passed under the inguinal ligament. Applicants' argument is not persuasive. The tourniquet of Milas is "non-invasive" because it does not injure the leg. While the tourniquet passed under the inguinal ligament is in the surgical field, the tourniquet does not injure the leg, does not go inside the leg, and is not applied directly to blood vessels of the leg.

Double Patenting

The rejection of claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,627,616 has been withdrawn in view of the amendment to the claims. However, the claims as amended are newly rejected using the '616 patent below.

8. Claims 1-3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36 and 39-42 remain rejected under the judicially created doctrine of obviousness-type double patenting as being

unpatentable over claim 1 of U.S. Patent No. 6,265,387 in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) for reasons of record.

Wolff claimed delivering naked plasmid DNA to a bile duct, increasing the permeability of the bile duct and obtaining delivery and expression in the liver. Wolff did not claim delivering DNA to skeletal muscle as claimed.

However, Wolff taught clamps applied to the femoral artery increased permeability of the artery and taught delivering naked plasmid DNA to a clamped femoral artery and obtaining expression in the quadriceps (col. 17, Example 8). Some of the animals received subcutaneous administration of dexamethasone the day before surgery (col. 18, line 45), which is an immunosuppressive drug as claimed.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into a vessel, increasing permeability and obtaining expression as claimed by Wolff wherein the vessel was a femoral artery, the permeability was increased using clamps and the DNA was delivered to skeletal muscle as taught in the specification of Wolff. One of ordinary skill in the art at the time the invention was made would have been motivated to inject the femoral artery instead of the bile duct as suggested in the specification of Wolff. One of ordinary skill in the art at the time the invention was made would have been motivated to use clamps to increase permeability in light of the disclosure of Wolff. One of ordinary skill in the art at the time the invention was made would have been

motivated to deliver DNA to skeletal muscle instead of the liver as in claim 1 of Wolff because Wolff suggested delivering DNA to skeletal muscle cells. The combined teachings of the claim and disclosure of Wolff did not teach using a tourniquet.

Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the skin of the leg and passed under the inguinal ligament (pg 2198, Fig. 1A, see tourniquet on rat and legend of Fig. 1B).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into the femoral artery of a rat using pressure to deliver the DNA to the quadriceps as taught by the combined teachings of the claim and disclosure of Wolff using a tourniquet as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using clamps with using the tourniquet of Milas to reduce damage to the blood vessel and to eliminate time in surgery spent applying clamps. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the adenoviral vector of Milas with naked plasmid DNA to prevent viral infection.

Applicants argue the claims require impeding the blood flow to and from the limb and point out that the method of Milas allows outflow of blood because a perfusion pump is used. Therefore, applicants conclude Milas does not meet the limitations of the claims. Applicants' arguments are not persuasive. The claims are not limited to

impeding all blood flow into and out of the limb. The tourniquet of Milas most definitely impedes blood flow into and out of the limb because it constricts the limb. While Milas used a perfusion pump to allow some blood flow out of the limb, the claims do not exclude allowing some blood flow out of the limb.

Applicants argue the tourniquet of Milas is not "non-invasive" as claimed because it passed under the inguinal ligament. Applicants' argument is not persuasive. The tourniquet of Milas is "non-invasive" because it does not injure the leg. While the tourniquet passed under the inguinal ligament is in the surgical field, the tourniquet does not injure the leg, does not go inside the leg, and is not applied directly to blood vessels of the leg.

9. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 as newly amended are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,627,616 in view of the disclosure of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) for reasons of record.

Claim 2 of '616 requires injecting naked DNA into a blood vessel and increasing the permeability of the blood vessel by increasing the pressure inside the vessel and obtaining delivery to cells outside of the blood vessel. Claim 3 requires inserting papaverine into the blood vessel. '616 did not claim delivering DNA to skeletal muscle as claimed.

However, '616 taught injecting plasmid DNA into the iliac artery using clamps "to block both the outflow and inflow of the blood to the leg" and L-NMMA and obtaining expression in the quadriceps (col. 9, lines 23-44).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into a blood vessel, increasing permeability and obtaining delivering the DNA to a cell outside of the blood vessel as claimed in '616 wherein the vessel was the iliac artery, the permeability was increased using clamps and L-NMMA the DNA was delivered and expressed in the quadriceps as taught in the specification of '616. One of ordinary skill in the art at the time the invention was made would have been motivated to inject the iliac artery because the specification of '616 expressly taught injecting the iliac artery was part of the invention. One of ordinary skill in the art at the time the invention was made would have been motivated to "block both the outflow and inflow of the blood to the leg" because the specification of '616 expressly taught blocking both the outflow and inflow of the blood to the leg was part of the invention. The combined teachings of the claim and disclosure of Wolff did not teach using a tourniquet.

Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the skin of the leg and passed under the inguinal ligament (pg 2198, Fig. 1A, see tourniquet on rat and legend of Fig. 1B).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into the iliac artery of a rat using pressure and L-NMMA to deliver the DNA to the quadriceps as taught by the combined teachings of the claim and disclosure of '616 using a tourniquet as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using clamps of '616 with using the tourniquet of Milas to reduce damage to the blood vessel and to eliminate time in surgery spent applying clamps. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the adenoviral vector of Milas with naked plasmid DNA to prevent viral infection.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER